# PREOPERATIVE EVALUATION OF CARDIOPULMONARY RESERVE WITH THE USE OF EXPIRED GAS ANALYSIS DURING EXERCISE TESTING IN PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE THORACIC ESOPHAGUS

Yoshinori Nagamatsu, MD[a]
Ichirou Shima, MD[a]
Hideaki Yamana, MD[b]
Hiromasa Fujita, MD[b]
Kazuo Shirouzu, MD[b]
Tatsuya Ishitake, MD[c]

**Objective:** We evaluated the usefulness of analyzing expired gas during exercise testing for the prediction of postoperative cardiopulmonary complications in patients with esophageal carcinoma.

**Background data:** Radical esophagectomy with 3-field lymphadenectomy is performed in patients with thoracic esophageal carcinoma but has a high risk of postoperative complications. To reduce the surgical risk, we performed preoperative risk analysis using 8 factors. Although hospital mortality was decreased when this risk analysis was used, severe cardiopulmonary complications still occurred.

**Methods:** The study group consisted of 91 patients who had undergone curative esophagectomy with 3-field lymphadenectomy. The maximum oxygen uptake, anaerobic threshold, vital capacity, percent vital capacity, forced expiratory volume in 1 second, percent forced expiratory volume, $\dot{V}_{25}$/HT, forced expired flow at 75% of forced vital capacity to height ratio ($FEF_{75\%}$/HT), forced expired flow at 50% to 75% of forced vital capacity ratio ($FEF_{50\%}/FEF_{75\%}$), percent diffusion capacity for carbon monoxide, and arterial oxygen tension were measured. Patients were divided into 2 groups on the basis of the presence or absence of postoperative cardiopulmonary complications.

**Results:** Only the maximum oxygen uptake was significantly different between the 2 groups. All patients were grouped according to the value of the maximum oxygen uptake, and the occurrence of postoperative cardiopulmonary complications was calculated for each group. A cardiopulmonary complication rate of 86% was found for patients with a maximum oxygen uptake of less than 699 mL $\cdot$ min$^{-1}$ $\cdot$ m$^{-2}$; for those with a value of 700 to 799 mL $\cdot$ min$^{-1}$ $\cdot$ m$^{-2}$, the complication rate was 44%.

**Conclusions:** The maximum oxygen uptake obtained by expired gas analysis during exercise testing correlates with the postoperative cardiopulmonary complication rate. On the basis of these results, esophagectomy with 3-field lymphadenectomy can be safely performed in patients with a maximum oxygen uptake of at least 800 mL $\cdot$ min$^{-1}$ $\cdot$ m$^{-2}$. (J Thorac Cardiovasc Surg 2001;121:1064-8)

The preferred treatment for carcinoma of the esophagus is surgical resection. For this treatment, many surgical approaches have been used, including esophagectomy without thoracotomy, esophagectomy with 2-field lymphadenectomy (thoracoabdominal lymph node dissection), and esophagectomy with 3-field lymphadenectomy (cervicothoracoabdominal lymph node dissection) via a right thoracotomy.[1-4] We routinely perform radical esophagectomy with 3-field lymphadenectomy for patients with squamous cell carcinoma involving the thoracic esophagus. This 3-field lymphadenectomy has been performed in 70% of the patients who have undergone radical surgery, but it is associated with a high risk of postoperative complications. To reduce the surgical

From the Department of Surgery, Saiseikai Yahata General Hospital, Kitakyushu,[a] and the Departments of Surgery[b] and Environmental Medicine,[c] Kurume University, School of Medicine, Kurume, Fukuoka, Japan.



0022-5223/2001 $35.00 + 0 **12/1/113596**
doi:10.1067/mtc.2001.113596

**Table I.** *Expired gas analysis during exercise testing in patients undergoing thoracic esophagectomy*

| *Cardiopulmonary complications* | *Present* | *Absent* | P *value* |
|---|---|---|---|
| $\dot{V}O_2max/m^2$ (mL · min$^{-1}$ · m$^{-2}$) | 789 ± 152 | 966 ± 124 | < .001 |
| AT/m$^2$ (mL · min$^{-1}$ · m$^{-2}$) | 488 ± 121 | 436 ± 138 | .12 |

*$Vo_2max$,* Maximum oxygen uptake; *AT,* anaerobic threshold.

risk, we have performed preoperative risk analysis based on 8 factors: age, pulmonary function testing with spirometry, cardiac function, renal function, liver function, 75 g oral glucose tolerance testing, depth of tumor invasion (T factor), and type of operative procedure. Although hospital mortality has been reduced from 13% to 3% with the use of this risk analysis, severe cardiopulmonary complications still occur.[5] Therefore, we have developed a preoperative risk assessment based on expired gas analysis during exercise testing. Several reports have suggested that this test is useful for preoperative screening of cardiopulmonary reserve in patients undergoing thoracic surgery.[6,7] The purpose of this study was to evaluate the usefulness of this test for the prediction of postoperative cardiopulmonary complications in patients with esophageal carcinoma undergoing radical esophagectomy.

## Methods

The study group consisted of 91 patients (88 men and 3 women) who had undergone curative esophagectomy with cervicothoracoabdominal 3-field lymphadenectomy via a right thoracotomy for squamous cell carcinoma of the thoracic esophagus between 1991 and 1995 at Kurume University Hospital. Their mean age was 59 years (range 38-74 years). All patients were smokers and they had no preoperative or postoperative operative adjuvant therapy. The pathologic staging of the cancer was stage I in 14 patients, stage IIa in 11 patients, stage IIb in 8 patients, stage III in 28 patients, and stage IVa in 30 patients (International Union Against Cancer–pTNM classification[8]). The expired gas analysis during exercise testing, spirometry, and flow-volume curve analysis were performed 7 days before the operation. Patients who had a medical history of heart failure, chronic obstructive pulmonary disease, or ischemic change by Masters electrocardiograms were excluded in this study.

On the basis of the expired gas analysis during exercise testing, the maximum oxygen uptake ($\dot{V}O_2max$) and anaerobic threshold (AT) were measured. Vital capacity (VC), percent vital capacity (%VC), forced expiratory volume in 1 second ($FEV_{1.0}$), percent forced expiratory volume ($FEV_{1.0}\%$), forced expired flow at 75% of forced vital capacity to height ratio ($\dot{V}_{25}$/HT), and forced expired flow at 50% to 75% of forced vital capacity ratio ($\dot{V}_{50}/\dot{V}_{25}$) were measured by spirometry or flow-volume curve analysis. Furthermore, the percent diffusion capacity for carbon monoxide (%DLCO) and arterial oxygen tension ($PaO_2$) were also measured by blood gas analysis.

The values for $\dot{V}O_2max$, AT, VC, and $FEV_{1.0}$ were divided by the body surface area (in square meters) to minimize variability due to differences in physique, and the values for $\dot{V}O_2max/m^2$, AT/m$^2$, VC/m$^2$, and $FEV_{1.0}/m^2$ were used for this study.

The Energy Measurement System 2900 (Sensor Medics, Yorba Linda, Calif) was used for the expired gas analysis during exercise testing. Exercise was performed at a graded workload with a bicycle ergometer. The workload started at 30 watts and increased by 10 watts every 2 minutes. When the workload reached 60 watts, it was increased by 20 watts every 2 minutes until a Borg rating[9] greater than 16 was achieved.

Measurements of expired gas were performed every 20 seconds. The $\dot{V}O_2max$ was defined as the maximum value for $\dot{V}O_2$ during exercise. Subsequently, the value for the AT was determined by the V-slope method.[10]

The patients were divided into 2 groups on the basis of whether or not they had cardiopulmonary complications. The first group (n = 74) had no postoperative cardiopulmonary complications and the second (n = 17) had complications. Postoperative cardiopulmonary complications were defined as (1) more than 10 days of mechanical ventilatory support, (2) more than 3 days of continuous therapy for a pulmonary complication, or (3) more than 3 days of therapy for cardiac arrhythmias. The pulmonary complications included bronchorrhea in 9 patients, pneumonia in 7, pulmonary edema in 6, left pleural effusion in 3, empyema in 2, and adult respiratory distress syndrome in 1 patient. Three patients had arrhythmias necessitating medication. Some patients had more than 1 postoperative complication.

Date are expressed as mean ± standard deviation. Statistical analysis was performed with the SPSS computer program (SPSS, Inc, Chicago, Ill) and included the Student *t* test or Mann-Whitney *U* test of continuous variables. Multiple logistic regression was used to evaluate the following 7 variables for their associations with cardiopulmonary complications: $\dot{V}O_2max/m^2$, AT/m$^2$, VC/m$^2$, $FEV_{1.0}/m^2$, $\dot{V}_{50}/\dot{V}_{25}$, %DLCO, and $PaO_2$.

## Results

Table I summarizes the results of the expired gas analysis during exercise testing. $\dot{V}O_2max/m^2$ was lower

**Table II.** *Spirometry, flow-volume curve, %DLCO, and $Pa_{O_2}$ in patients undergoing thoracic esophagectomy*

| *Cardiopulmonary complications* | *Present* | *Absent* | P *value* |
|---|---|---|---|
| $VC/m^2$ ($mL/m^2$) | 2230 ± 501 | 2420 ± 412 | .12 |
| %VC (%) | 103 ± 21.0 | 112 ± 18.9 | .08 |
| $FEV_{1.0}/m^2$ ($mL/m^2$) | 1710 ± 431 | 1720 ± 330 | .99 |
| $FEV_{1.0}\%$ (%) | 76.8 ± 10.7 | 72.4 ± 11.7 | .16 |
| $\dot{V}_{25}/HT$ (mL/m) | 610 ± 357 | 446 ± 246 | .03 |
| $\dot{V}_{50}/\dot{V}_{25}$ | 3.22 ± 0.84 | 3.86 ± 1.49 | .1 |
| DLCO (%) | 110 ± 29.7 | 116 ± 27.7 | .4 |
| $Pa_{O_2}$ (mm Hg) | 91.6 ± 7.72 | 89.6 ± 8.89 | .4 |

*VC,* vital capacity; *$FEV_{1.0}$,* forced expiratory volume in 1 second; *$\dot{V}_{25}/HT$*, forced expired flow at 75% of forced vital capacity to height ratio; *$\dot{V}_{50}/\dot{V}_{25}$*, forced expired flow at 50% to 75% of forced vital capacity ratio; *DLCO,* diffusion capacity for carbon monoxide.

**Table III.** *Analysis of 7 major variables with logistic regression procedure*

| *Variable* | β | $\chi^2$ | P *value* |
|---|---|---|---|
| Intercept | 7.45 | | |
| $\dot{V}O_2max/m^2$ | –0.0195 | 14.75 | .0001 |
| $AT/m^2$ | 0.009 | 3.68 | .055 |
| $VC/m^2$ | –0.0012 | 0.52 | .5 |
| $FEV_{1.0}/m^2$ | 0.0028 | 2.04 | .15 |
| $\dot{V}_{50}/\dot{V}_{25}$ | –0.306 | 0.66 | .4 |
| %DLCO | 0.032 | 4.99 | .026 |
| $Pa_{O_2}$ | –0.0042 | 0.10 | .7 |

*$\dot{V}O_2max$,* Maximum oxygen uptake; *AT,* anaerobic threshold; *VC,* vital capacity; *$FEV_{1.0}$,* forced expiratory volume in 1 second; *$\dot{V}_{25}/HT$*, forced expired flow at 75% of forced vital capacity to height ratio; *$\dot{V}_{50}/\dot{V}_{25}$*, forced expired flow at 50% to 75% of forced vital capacity ratio; *DLCO,* diffusion capacity for carbon monoxide.

among patients having cardiopulmonary complications ($P < .0001$). However, the values for $AT/m^2$ were similar ($P = .12$). Table II summarizes the results of spirometry, flow-volume curve analysis, %DLCO, and $Pa_{O_2}$. The values for $VC/m^2$, %VC, $FEV_{1.0}/m^2$, $FEV_{1.0}\%$, $\dot{V}_{50}/\dot{V}_{25}$, %DLCO, and $Pa_{O_2}$ were not significantly different between the 2 groups. The values for $\dot{V}_{25}/HT$ were higher among patients having cardiopulmonary complications ($P = .03$).

Next, the order of importance of 7 variables was evaluated by logistic regression (Table III). $\dot{V}O_2max/m^2$ and %DLCO were statistically significant. A receiver operating characteristic curve of $\dot{V}O_2max/m^2$ is shown in Fig 1. The inflection value of the receiver operating characteristic curve was 800 $mL \cdot min^{-1} \cdot m^{-2}$.

On the basis of these results, $\dot{V}O_2max/m^2$ was selected as a risk factor for the development of complications. All 91 patients were divided into 7 groups according to the value of their $\dot{V}O_2max/m^2$, and the occurrence of postoperative cardiopulmonary complications was calculated for each rank value (Fig 2). The rate of cardiopulmonary complications was 86% in patients with a $\dot{V}O_2max/m^2$ less than 699 $mL \cdot min^{-1} \cdot m^{-2}$, 44% in patients with a $\dot{V}O_2max/m^2$ of 700 to 799 $mL \cdot min^{-1} \cdot m^{-2}$, 10% in patients with a $\dot{V}O_2max/m^2$ of 800 to 1099 $mL \cdot min^{-1} \cdot m^{-2}$, and 0% in patients with a $\dot{V}O_2max/m^2$ of 1100 $mL \cdot min^{-1} \cdot m^{-2}$ or more.

## Discussion

Esophagectomy with cervicothoracoabdominal 3-field lymphadenectomy via right thoracotomy is currently performed in patients with squamous cell carcinoma involving the thoracic esophagus, and the long-term survival of patients with esophageal cancer has significantly improved.[11] However, because this type of surgery can have serious cardiopulmonary effects, not all patients are able to withstand such an operation. At our institution, we use the following criteria to decide which patients should undergo this operation: age less than 70 years, evidence that the procedure will be curative, no major organ dysfunction, and low risk for complications.

In risk analysis, scores are assigned for routine pulmonary function tests, cardiac function tests, renal function tests, liver function tests, and the probability of preservation of the right bronchial artery and the pulmonary branches of the right vagus nerve. It has been reported that postoperative mortality and hospital mortality can be decreased by risk analysis.[5]

The lymphatic network can be obstructed diffusely by 3-field dissection of the cervical, thoracic, and abdominal lymph nodes. This obstruction leads to considerable fluid accumulation in the third space and places a great burden on the cardiopulmonary system as the fluid re-enters the bloodstream postoperatively.

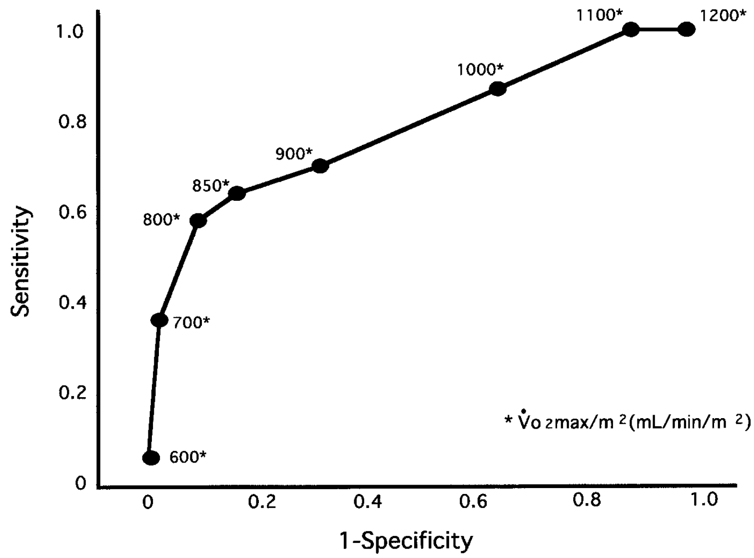


**Fig 1.** A receiver operating characteristic curve of $\dot{V}O_2$max/m$^2$.

Therefore, there is a high risk of serious cardiopulmonary complications when 3-field lymphadenectomy is performed in patients with a decreased cardiopulmonary reserve.

In the present study, we tested pulmonary function with spirometry, flow-volume curve analysis, measurement of the diffusing capacity, and blood gas analysis, but evaluation of actual cardiopulmonary reserve is impossible (Table II).

Therefore, we used expired gas analysis during exercise testing, which allows evaluation of cardiopulmonary reserve. Expired gas analysis during exercise testing is widely used in the field of exercise physiology and during the rehabilitation of patients with cardiovascular disease.

Recently, it has also been used for the preoperative determination of cardiopulmonary reserve in patients undergoing thoracic surgery[6,7,12,13] and for the evaluation of exercise capacity after lung cancer surgery.[14,15]

We studied 2 variables, $\dot{V}O_2$max/m$^2$ and AT/m$^2$, which can be determined by expired gas analysis during exercise testing. The $\dot{V}O_2$max represents the $\dot{V}O_2$ at the time of maximal workload and is the best index of exercise tolerance. The AT was defined by Wasserman and associates[16] and is determined by measuring the $\dot{V}O_2$ at an exercise intensity that can be maintained for at least 1 hour. In the present study, the $\dot{V}O_2$max closely correlated with the occurrence of postoperative cardiopulmonary complications. In contrast, the AT did not correlate with the occurrence of complications. These findings may be due to the fact that the cardiopulmonary burden of esophagectomy with 3-field lymphadenectomy is so great that it cannot be compared with the exercise workload determined by the AT. Consequently, postoperative cardiopulmonary complications could not be predicted by AT/m$^2$. However, because $\dot{V}O_2$max can be used for the evaluation of not only the cardiopulmonary reserve at high workloads, but also systemic and mental fitness, it appears to be closely correlated with the occurrence of postoperative cardiopulmonary complications.

On the basis of our results, we chose a minimally acceptable value of 800 mL/m$^2$ for the $\dot{V}O_2$max/m$^2$ for patients undergoing curative transthoracic esophagectomy. In a previous study of transthoracic lobectomy for lung cancer, we chose a minimally acceptable value of 700 mL/m$^2$ for $\dot{V}O_2$max/m$^2$.[7] The different values resulted from differences in the degree of surgical invasion and a direct insult to the lungs between transthoracic lobectomy and subtotal esophagectomy.

In the present study, we conducted a retrospective study to assess the prediction of postoperative cardiopulmonary complications using spirometry, flow-volume curve analysis, diffusing capacity, and expired gas analysis during exercise testing in patients undergoing curative esophagectomy via a right thoracotomy for squamous cell carcinoma of the thoracic esophagus. None of the routine pulmonary function tests correlated with the occurrence of postoperative cardiopulmonary complications, but the $\dot{V}O_2$max/m$^2$ correlated with the risk of postoperative cardiopulmonary complications.

Therefore, it was possible to predict postoperative cardiopulmonary complications that could not be determined by routine pulmonary function tests. On the

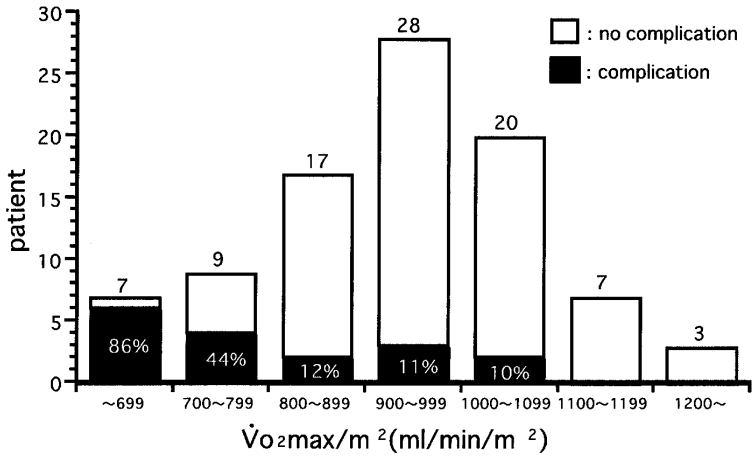


**Fig 2.** Occurrence rates for cardiopulmonary complications in patients undergoing thoracic esophagectomy based on their $\dot{V}O_2max/m^2$.

basis of the results of the present study, esophagectomy with cervicothoracoabdominal 3-field lymphadenectomy can be safely performed in patients with a $\dot{V}O_2max/m^2$ of at least 800 mL/m$^2$. So that postoperative cardiopulmonary complications can be avoided in patients with a $\dot{V}O_2max/m^2$ less than 800 mL/m$^2$, a 2-staged operation with less surgical invasion or esophagectomy without thoracotomy should be performed.

Received for publication Sept 30, 1999; revisions requested Nov 15, 1999; revisions received Nov 22, 2000; accepted for publication Nov 27, 2000.

Address for reprints: Yoshinori Nagamatsu, Department of Surgery, Saiseikai Yahata General Hospital, 5-9-27 Harunomachi Yahatahigashi-ku Kitakyushu City, 805-8527, Japan.

## REFERENCES

1. Fujita H, Kakegawa T, Yamana H, Shima I, Toh Y, Tomita Y, et al. Mortality and morbidity rates, postoperative course, quality of life, and prognosis after extended radical lymphadenectomy for esophageal cancer: comparison of three-field lymphadenectomy with two-field lymphadenectomy. Ann Surg 1995;222:654-62.
2. Akiyama H, Tsurumaru M, Udagawa H, Kajiyana Y. Radical lymph node dissection for cancer of the thoracic esophagus. Ann Surg 1994;220:364-73.
3. Baba M, Aikou T, Yoshinaka H, Natsugoe S, Fukumoto T, Shimazu H, et al. Long-term results of subtotal esophagectomy with three-field lymphadenectomy for carcinoma of the thoracic esophagus. Ann Surg 1994;219:310-6.
4. Altorki NK, Skinner DB. Occult cervical nodal metastasis in esophageal cancer: preliminary results of three-field lymphadenectomy. J Thorac Cardiovasc Surg 1997;113:540-4.
5. Zhang G-H, Fujita H, Yamana H, Kakegawa T. A prediction of hospital mortality after surgical treatment for esophageal cancer. Surg Today Jpn J Surg 1994;24:122-7.
6. Nagamatsu Y, Takamori S, Hayashida R, Yamana H, Shirouzu K. Pulmonary capacity in lung cancer patients prior to lung resection: comparison of the unilateral pulmonary artery occlusion test with expired gas analysis during exercise testing. Kurume Med J 1996;43:273-7.
7. Nagamatsu Y, Ono H, Hiraki H, Matsuo T, Mitsuoka M, Takamori S, et al. Pre-operative screening test for lung cancer using the analysis of expired gas with exercise testing—principally $\dot{V}O_2max/m^2$ (in Japanese with English abstract). J Jpn Assoc Thorac Surg (Nippon Kyoubu Geka Gakkai Zasshi) 1994;42:1910-5.
8. Hermanek P, Sobin LH, editors. International Union Against Cancer: TNM classification of malignant tumours. 4th ed, 2nd rev. Berlin: Springer-Verlag; 1992.
9. Borg G. Perceived exertion as an indicator of somatic stress. Scand J Rehabil Med 1970:2-3;92-8.
10. Weber KT, Janicki JS. Cardiopulmonary exercise testing. Philadelphia: WB Saunders; 1986: p. 15-33.
11. Kakegawa T, Fujita H, Yamana H. Illustration of surgery for carcinoma in the thoracic esophagus. In: Sato T, Iizuka T, editors. Color atlas of surgical anatomy for esophageal cancer. Tokyo: Springer-Verlag; 1992. p. 91-114.
12. Eugene J, Brown SE, Light RW, Milne NE, Stemmer EA. Maximum oxygen consumption: a physiologic guide to pulmonary resection. Surg Forum 1982;33:260-2.
13. Smith TP, Kinasewitz GT, Tucker WY, Spillers WP, George RB. Exercise capacity as a predictor of post-thoracotomy morbidity. Am Rev Respir Dis 1984;129:730-4.
14. Nagamatsu y, Ono H, Tsushimi M, Matsuo T, Hiraki H, Hayashi A, et al. Exercise capacity evaluation after pulmonary resection: exercise test and expired gas analysis (in Japanese with English abstract). J Jpn Assoc Chest Surg (Nippon Kokyuki Geka Gakkai Zasshi) 1993;7:770-5.
15. Nagamatsu Y, Ono H, Hiraki H, Matsuo T, Fukuda M, Mitsuoka M, et al. Evaluation of the exercise capacity recovery process after lung cancer surgery by exercise test and expired gas analysis (in Japanese with English abstract). J Jpn Assn Thorac Surg (Nippon Kyoubu Geka Gakkai Zasshi) 1994;42:228-32.
16. Wasserman K, Whipp BJ, Koyal SN, Beaver WL. Anaerobic threshold and respiratory gas exchange during exercise. J Appl Physiol 1973;35:236-43.